We claim:

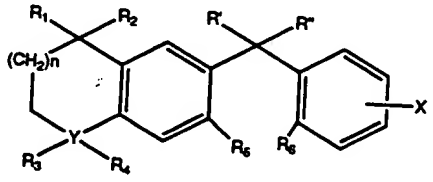
1. A ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors.

2. A ligand which modulates a process selectively mediated by Retinoid X Receptors in preference to Retinoic Acid Receptors.

3. The ligand of claim 1 wherein said ligand is at least five-fold more potent an activator of Retinoid X Receptors than of Retinoic Acid Receptors.

4. The ligand of claim 3 wherein said ligand has an efficacy of less than 20% for Retinoic Acid Receptors.

5. A compound having the formula:



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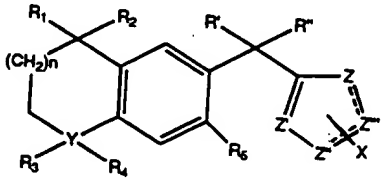

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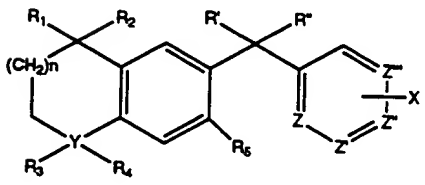

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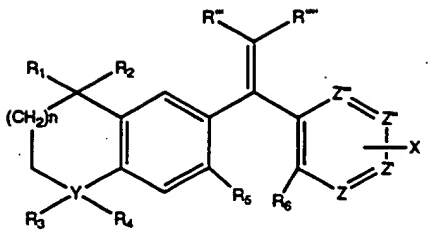

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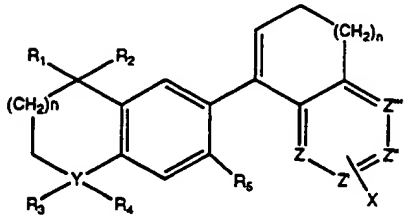

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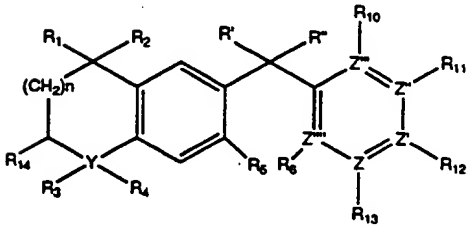

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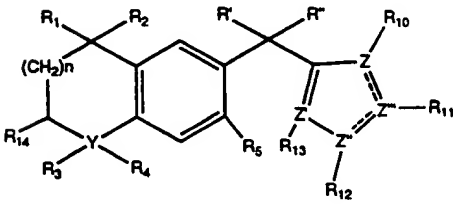


wherein

R_1 and R_2, each independently, represent hydrogen or lower alkyl or acyl having 1-4 carbon atoms;

Y represents C, O, S, N, CHOH, CO, SO, SO_2, or a pharmaceutically acceptable salt;

R_3 represents hydrogen or lower alkyl having 1-4 carbon atoms where Y is C or N;

R_4 represents hydrogen or lower alkyl having 1-4 carbon atoms where Y is C, but R_4 does not exist if Y is N, and neither R_3 or R_4 exist if Y is S, O, CHOH, CO, SO, or SO_2;

R′ and R″ represent hydrogen, lower alkyl or acyl having 1-4 carbon atoms, OH, alkoxy having 1-4 carbon atoms, thiol or thio ether, or amino,

or R′ or R″ taken together form an oxo (keto), methano, thioketo, HO-N=, NC-N=, (R_7R_8)N-N=, epoxy, cyclopropyl, or cycloalkyl group and wherein the epoxy, cyclopropyl, and cycloalkyl groups can be substituted with lower alkyl having 1-4 carbons or halogen;

R′″ and R″″ represent hydrogen, halogen, lower alkyl or acyl having 1-4 carbon atoms,

or R′″ and R″″ taken together form a cycloalkyl group having 3-10 carbons, and wherein the cycloalkyl group can be substituted with lower alkyl having 1-4 carbons or halogen;

R_5 represents hydrogen, a lower alkyl having 1-4 carbons, halogen, nitro, OR_7, SR_7, NR_7R_8, or $(CF)_nCF_3$, but R_5 cannot be hydrogen if together R_6, R_{10}, R_{11}, R_{12} and R_{13} are all hydrogen and Z, Z′, Z″, Z′″, or Z″″ are all carbon;

R_6, R_{10}, R_{11}, R_{12}, R_{13} each independently represent hydrogen, a lower alkyl having 1-4 carbons, halogen, nitro, OR_7, SR_7, NR_7R_8 or

$(CF)_nCF_3$, and exist only if the Z, Z', Z", Z'", or Z"" from which it originates is C, or each independently represent hydrogen or a lower alkyl having 1-4 carbons if the Z, Z', Z", Z'", or Z"" from which it originates is N, and where one of R_6, R_{10}, R_{11}, R_{12} or R_{13} is X;

R_7 represents hydrogen or a lower alkyl having 1-6 carbons;

R_8 represents hydrogen or a lower alkyl having 1-6 carbons;

R_{14} represents hydrogen, a lower alkyl having 1-4 carbons, oxo, hydroxy, acyl having 1-4 carbons, halogen, thiol, or thioketone;

X is COOH, tetrazole, PO_3H, SO_3H, CHO, CH_2OH, $CONH_2$, COSH, $COOR_9$, $COSR_9$, $CONHR_9$, or COOW where R_9 represents a lower alkyl having 1-4 carbons, phenyl, aromatic alkyl, or q-hydroxyphenyl, q-bromophenyl, q-chlorophenyl, q-florophenyl, or q-iodophenyl, where q=2-4, where W is a pharmaceutically acceptable salt, and where X can originate from any C or N on the ring;

Z, Z', Z", Z"' and Z"", each independently, represent C, S, O, N, or a pharmaceutically acceptable salt, but is not O or S if attached by a double bond to another such Z or if attached to another such Z which is O or S, and is not N if attached by a single bond to another such Z which is N;

n = 0-3; and

the dashed lines in the second and seventh structures shown depict optional double bonds.

6. A compound of claim 5 wherein said compound selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors.

7. A compound selected from the group consisting of 4-[(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoic acid,

4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid,

4-[1-(3-5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]benzoic acid,

4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzenetetrazole,

2-[1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylic acid,

2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylic acid,

ethyl 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylate,

5-[1-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-2-carboxylic acid,

2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylic acid,

methyl 2-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylate, and

4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]-N-(4-hydroxyphenyl)benzamide.

8. 4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]benzoic acid.

9. 2-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]pyridine-5-carboxylic acid.

10. 2-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)cyclopropyl]pyridine-5-carboxylic acid.

11. A pharmaceutical composition comprising in a

pharmaceutically acceptable vehicle suitable for enteral, parenteral, or topical administration, one or more compound of claim 2.

12. A pharmaceutical composition comprising in a pharmaceutically acceptable vehicle suitable for enteral, parenteral, or topical administration, one or more compound of claim 5.

13. A method for modulating a process selectively mediated by one or more Retinoid X Receptors, said method comprising causing said process to be conducted in the presence of a ligand which selectively activates one or more said Retinoid X Receptors in preference to Retinoic Acid Receptors.

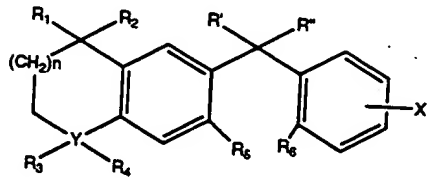
14. The method of claim 13 wherein said ligand is at least five-fold more potent an activator of Retinoic Acid Receptors than of Retinoic Acid Receptors.

15. The method of claim 14 wherein said ligand has an efficacy of less than 20% for Retinoic Acid Receptors.

16. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising causing said process to be conducted in the presence of at least one ligand as set forth in claim 2.

17. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising causing said process to be conducted in the presence of at least one compound as set forth in claim 5.

18. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising causing said process to be conducted in the presence of at least one compound of the formula:



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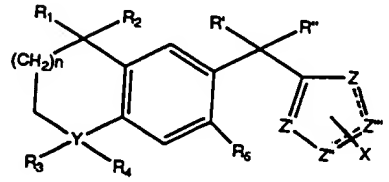

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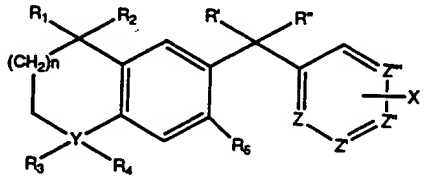

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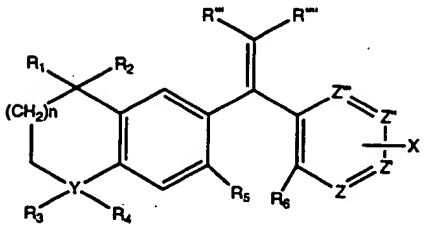

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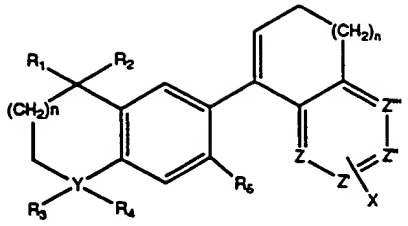

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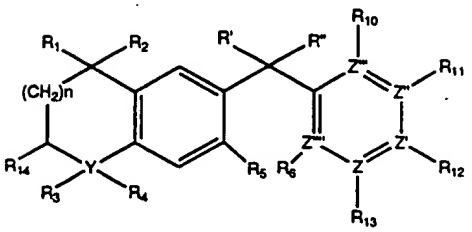

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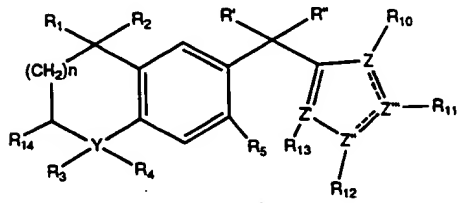

wherein

R_1 and R_2, each independently, represent hydrogen or lower alkyl or acyl having 1-4 carbon atoms;

Y represents C, O, S, N, CHOH, CO, SO, SO_2, or a pharmaceutically acceptable salt;

R_3 represents hydrogen or lower alkyl having 1-4 carbon atoms where Y is C or N;

R_4 represents hydrogen or lower alkyl having 1-4 carbon atoms where Y is C, but R_4 does not exist if Y is N, and neither R_3 or R_4 exist if Y is S, O, CHOH, CO, SO, or SO_2;

R′ and R″ represent hydrogen, lower alkyl or acyl having 1-4 carbon atoms, OH, alkoxy having 1-4 carbon atoms, thiol or thio ether, or amino,

or R′ or R″ taken together form an oxo (keto), methano, thioketo, HO-N=, NC-N=, (R_7R_8)N-N=, epoxy, cyclopropyl, or cycloalkyl group and wherein the epoxy, cyclopropyl, and cycloalkyl groups can be substituted with lower alkyl having 1-4 carbons or halogen;

R′″ and R″″ represent hydrogen, halogen, lower alkyl or acyl having 1-4 carbon atoms,

or R′″ and R″″ taken together form a cycloalkyl group having 3-10 carbons, and wherein the cycloalkyl group can be substituted with lower alkyl having 1-4 carbons or halogen;

R_5 represents hydrogen, a lower alkyl having 1-4 carbons, halogen, nitro, OR_7, SR_7, NR_7R_8, or $(CF)_nCF_3$, but R_5 cannot be hydrogen if together R_6, R_{10}, R_{11}, R_{12} and R_{13} are all hydrogen and Z, Z′, Z″, Z′″, or Z″″ are all carbon;

R_6, R_{10}, R_{11}, R_{12}, R_{13} each independently represent hydrogen, a lower alkyl having 1-4 carbons, halogen, nitro, OR_7, SR_7, NR_7R_8 or $(CF)_nCF_3$, and exist only if the Z, Z′, Z″, Z′″, or Z″″ from which it originates is C, or each independently represent hydrogen or a lower alkyl having 1-4 carbons if the Z, Z′, Z″, Z′″, or Z″″ from which it originates is N, and where one of R_6, R_{10}, R_{11}, R_{12} or R_{13} is X;

R_7 represents hydrogen or a lower alkyl having 1-6 carbons;

R_8 represents hydrogen or a lower alkyl having 1-6 carbons;

R_{14} represents hydrogen, a lower alkyl having 1-4 carbons, oxo, hydroxy, acyl having 1-4 carbons, halogen, thiol, or thioketone;

X is COOH, tetrazole, PO_3H, SO_3H, CHO, CH_2OH, $CONH_2$, COSH, $COOR_9$, $COSR_9$, $CONHR_9$, or COOW where R_9 represents a lower alkyl having 1-4 carbons, phenyl, aromatic alkyl, or q-hydroxyphenyl, q-bromophenyl, q-chlorophenyl, q-florophenyl, or q-iodophenyl, where q=2-4, where W is a pharmaceutically acceptable salt, and where X can originate from any C or N on the ring;

Z, Z', Z", Z"' and Z"", each independently, represent C, S, O, N, or a pharmaceutically acceptable salt, but is not O or S if attached by a double bond to another such Z or if attached to another such Z which is O or S, and is not N if attached by a single bond to another such Z which is N;

n = 0-3; and

the dashed lines in the second and seventh structures shown depict optional double bonds.

19. A method according to claim 18 wherein said Retinoid X Receptor is Retinoid X Receptor-alpha, Retinoid X Receptor-beta, or Retinoid X Receptor-gamma.

20. A method according to claim 18 wherein said process is the *in vivo* modulation of lipid metabolism, *in vivo* modulation of skin-related processes, *in vivo* modulation of malignant cell development, or *in vivo* modulation of premalignant lesions.

21. A method according to claim 18 wherein said process is *in vitro* cellular growth and differentiation, or *in vivo* limb morphogenesis.

22. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising causing said process to be conducted in the presence of at least one compound as set forth in claim 7.

23. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising administering to a mammalian subject an amount, effective to modulate said process

mediated by said one or more Retinoid X Receptors, of one or more ligand of claim 2.

24. A method for modulating a process mediated by one or more Retinoid X Receptors, said method comprising administering to a mammalian subject an amount, effective to modulate said process mediated by said one or more Retinoid X Receptors, of one or more compound of claim 5.

25. A method for treating a mammalian subject requiring Retinoid X Receptor therapy comprising administering to such subject a pharmaceutically effective amount of one or more ligands as set forth in claim 2.

26. A method for treating a mammalian subject requiring Retinoid X Receptor therapy comprising administering to such subject a pharmaceutically effective amount of one or more compounds as set forth in claim 5.

27. A method for increasing plasma concentrations of high density lipoprotein in a mammalian subject comprising administering to such subject a pharmaceutically effective amount of one or more ligands as set forth in claim 5.

28. A method for determining the presence of one or more Retinoid X Receptors comprising combining a compound of claim 5 with a sample containing one or more unknown receptors and determining whether said ligand binds to any receptor in said sample.

29. A method of purifying Retinoid X Receptors comprising combining a compound as set forth in claim 5 with a sample containing one or more said Retinoid X Receptors, allowing said compound to bind with Retinoid X Receptors, and separating out the bound combination of said compound and Retinoid X Receptor.

30. A composition comprising a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which selectively activates Retinoic Acid Receptors in preference to Retinoid X Receptors.

31. A composition comprising a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which activates one or more intracellular receptors other than Retinoid X Receptors.

32. The composition of claim 30 or 31 wherein the physiological effect in mammals produced by said composition at a given concentration is greater than the additive effect achieved utilizing each said ligand alone at said concentration.

33. A pharmaceutical composition comprising in a pharmaceutically acceptable vehicle for enteral, parenteral, or topical administration a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which selectively activates one or more intracellular receptors other than Retinoid X Receptors.

34. A pharmaceutical composition of claim 33 wherein said second ligand selectively activates Retinoic Acid Receptors in preference to Retinoid X Receptors.

35. A method for modulating a process mediated by intracellular receptors, said method comprising causing said process to be conducted in the presence of a composition comprising a first ligand which selectively activates Retinoid X Receptors in preference to Retinoic Acid Receptors, in combination with a second ligand which activates one or more intracellular receptors other than Retinoid X Receptors, and wherein the physiological effect in mammals produced by said composition at a given concentration is greater than the additive effect achieved utilizing each said ligand alone at said concentration.

36. The method of claim 35 wherein said second ligand selectively activates Retinoic Acid Receptors in preference to Retinoid X Receptors.

37. The method of claim 36 wherein said process is the *in vivo* modulation of lipid metabolism, *in vivo* modulation of skin-related processes, *in vivo* modulation of malignant cell development, *in vivo* modulation of premalignant lesions, or *in vivo* modulation of programmed cell death.

38. The method of claim 35 wherein said composition is present at a concentration at which neither said first nor second ligand would alone produce a significant therapeutic response.

39. The method of claim 35 wherein said second ligand activates peroxisome proliferator activated receptors.

40. The method of claim 35 wherein said second ligand activates Vitamin D receptors.

41. The method of claim 35 wherein said second ligand activates thyroid hormone receptors, HNF4 receptors, or members of the COUP family of receptors.